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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,178	06/18/2001	Nobuo Nagai	702-010411	5455

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 04/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,178	NAGAI ET AL.	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *7 and 12-14* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5 September 2004 (filed 3 March 2004) has been entered.

Status of Amendments

2. The Preliminary Amendment filed 38 March 2001 has been received and entered.

Withdrawn of Objections And/Or Rejections

3. The Objection to the Specification as set forth at pp. 3 ¶7 in the previous Office Action (5 May 2003) is *moot* in view of the Preliminary Amendment filed 28 March 2001 and the Amendment filed 24 March 2003.

4. The Rejection of claim **15** under 35 U.S.C. §112 ¶1 as set forth at pp. 3 ¶8 in the previous Office Action (5 May 2003) is *moot* in view of Applicant's cancellation of said claim (5 September 2003).

5. The Rejection of claims **7** and **12-14** under 35 U.S.C. §112 ¶1 as set forth at pp. 3-7 ¶9-19 in the previous Office Action (5 May 2003) is *withdrawn* in view of the Declaration by filed

on 5 September 2003. A revised rejection is included herein to take the Declaration into consideration.

6. The Declaration by filed on 5 September 2003 is sufficient to overcome the rejection of claims **7** and **12-14** under 35 U.S.C. §102(b) as set forth at pp. 7-9 ¶19-22 in the previous Office Action (5 May 2003).

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims **7** and **12-14** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method for the treatment of focal cerebral ischemic infraction by administering an effective dosage of at least one α_2-antiplasmin neutralizing protein selected from the group consisting of plasmin, mini-plasmin, and microplasmin*, does not reasonably provide enablement for *practicing said method using other α_2-antiplasmin neutralizing compounds, mutants, and hybrids thereof.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

8. The claims are drawn very broadly to methods of using any given compound with α_2-antiplasmin neutralizing activity. The language of said claims encompasses chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetic, transformed cells, radiation, antibodies, antibody fragments, cyclic peptides, agonists, antagonists, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds.

9. The specification teaches that injection of 50, 100 or 15Q μg human plasmin (Pli) in mice weighing approximately 30 g decreased the α_2-AP (α_2-antiplasmin) levels in blood samples taken after 30s to 67, 40, and 31% of baseline, respectively. Injection of 200 μg Pli in 3 mice reduced the plasma α_2-AP levels to 59, 67, and 70% after 2, 4, and 6 hours respectively. Ligation of the left middle cerebral artery (MCA) induced a cerebral infarct with a volume of 27 ± 1.3 mm^3 (n= 10) in inbred Balb/c mice, and of 16 ± 1.3 mm^3 (n= 12) in inbred C57BL/6 mice. Injection of 0.2 mg Pli in Balb/c mice reduced the infarct size to 22 + 1.0 mm^3 (n= 9). Similar decreases were observed when the Pli injection was given 15 min before or 15 min after ligation of the MCA (Table 1). In CS7B1/6 mice, injection of 0.2 mg Pli 40 reduced the infarct size to 10 ± 1.2 mm^3 (n= 12).

10. However, the specification fails to provide any guidance for the successful manufacture of use of other α_2-antiplasmin neutralizing compounds. Since resolution of the various complications in regards to targeting a particular enzyme in an organism with any one of a myriad of candidate compounds is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In

order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations of unknown α_2-antiplasmin neutralizing compounds. These compositions would then have to be tested in a cerebral infract model, evaluated for any and all related proteins, signs, and symptoms to correlate with the effectiveness of plasmin, miniplasmin, and microplasmin. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

11. Additionally, a person skilled in the art would recognize that predicting the efficacy of using any given compound that may or may not have α_2-antiplasmin neutralizing activity *in vivo* based solely on the performance of unrelated proteins (plasmin, miniplasmin, and microplasmin) as highly problematic (see MPEP §2164.01). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo*, such a disclosure would not be considered enabling since the state of protein biochemistry and enzyme inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

12. The following references are cited herein to illustrate the state of the art of protein biochemistry and α_2-antiplasmin.

13. Regarding derivatives and fragments of α_2-antiplasmin neutralizing polypeptides, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 433-506]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of

active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to

recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

14. On the level of predictability in the art, Smalling (15 November 1997) "A fresh look at the molecular pharmacology of plasminogen activators: From theory to test tube to clinical outcomes." Am. J. Health-Syst. Pharm. 54(Suppl. 1): S17-S22 teaches that thrombolytic agents are confronted by two complexities, the administration protocol and the half-life of the molecule. A thrombolytic agent must last long enough to be effective but not too long as to cause undue bleeding in a patient (pp. S18). Also, mutations of the tissue plasminogen activator molecule, ranging from deletions to point mutations varying in their effectiveness and half-life (Figure 1-3). Thus absent specific mutations or modifications of plasmin which may have the desired activity, a skilled artisan cannot predict the usefulness of any given mutant or hybrid absent experimentation.

15. Furthermore on the predictability of the art, Reddy (January 1998) "Newer Thrombolytic drugs for acute myocardial infarction." Indian Journal of Experimental Biology 36(1): 1-15 provides guidance on several mutations and altered plasminogen derivatives (pp. 3-12). However, Reddy notes the despite the ease with which mutations can be made, their *in vivo* activity, specificity, and half-life are by no means guaranteed leaving a significant burden on the skilled artisan to determine which mutations and derivatives of plasminogen are useful to satisfy the preambles of the claims (pp. 12-13).

16. On the quantity of experimentation needed to practice the invention to its full scope, Bell (1997) "Evaluation of Thrombolytic Agents." Drugs 54(Supplement 3): 11-17 teaches that the undertaking of identifying and evaluating the efficacy of a thrombolytic agent is hampered by the

difficulty associated with the undesirable averse effects of the agents especially bleeding (pp. 14). Thus a skilled artisan is confronted with an undue burden of experimentation to insure that the "mutants and hybrids" as claimed fulfill the preamble of claim 7.

17. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *prophetic suggestion* to the *in vivo* administration of α_2-antiplasmin neutralizing compounds and/or treatment of focal cerebral ischemic infarction as exemplified in the references herein.

18. Claims **7, 13,** and **14** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

19. Claim 7 requires a "α_2-antiplasmin neutralizing compound" while practicing the claimed methods but does not require that the compound to possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Claims 13 and 14 require a "one Kringle domain and mutants and hybrids thereof" while practicing the claimed methods but does not require that the mutants and hybrids possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of agents that is defined by desired activity.

20. Furthermore the art recognizes that "compound" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetic, transformed cells, radiation, antibodies,

antibody fragments, cyclic peptides, agonists, antagonists, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds.

21. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a recitation of desired outcome. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

22. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement

"by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572.

23. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003) and *University of Rochester v. G.D. Searle & Co. et al.* CAFC [(03-1304) 13 February 2004]. In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting prostaglandin synthesis in human host using an unspecified compound, in order to relieve pain without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since the patent described the compound's desired function of reducing activity of the enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing "assays" to screen compounds in order to discover those with desired effect. The patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound. And since specification did not indicate that compounds are available in public depository, the claimed treatment method cannot be practiced without compound. Thus the inventors cannot be said to have "possessed" claimed invention without knowing of a compound or method certain to produce compound. Thus said patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

24. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Summary

25. No claims are allowed.

26. The following claims were drafted by the examiner and considered to distinguish patentably over the art of record in this application, are presented to applicant for consideration:

Claims 1-6 (Cancelled)

Claim 7 (Currently Amended) A method for treatment of focal cerebral ischemic infarction by administering in an effective dosage amount of between about 1.5 to 7.0 mg/kg of at least one α_2-antiplasmin neutralizing compound selected from the group consisting of plasmin, mini-plasmin (lacking the first four kringles), and micro-plasmin (lacking all five kringles).

Claims 8-15 (Cancelled)

27. The Examiner acknowledges that acceptance of the above proposed claims in any subsequent response and/or amendment do not mitigate in any way, shape, or form, Applicant's right to pursue additional subject matter in continuation, continuation-in-part, and/or divisional applications pursuant to 35 U.S.C. §120 and §121.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Elizabeth C. Kemmerer

CJN
April 21, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER